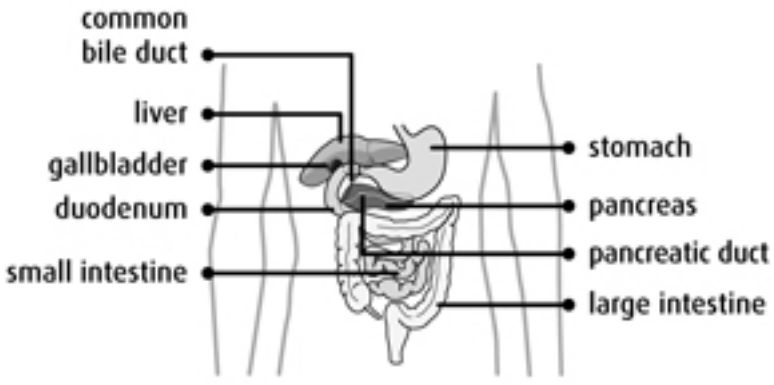
Pancreatic Cancer

Excerpt from www.cancer.ca:

Pancreatic cancer starts in the cells of the pancreas. The pancreas is a large gland that lies behind your stomach deep in the upper part of the abdomen.



The pancreas is part of the digestive system. Digestive juices made by the pancreas flow down a tube in the centre of the pancreas called the *pancreatic duct*. The pancreatic duct joins the common bile duct, which carries bile from the liver. The common bile duct then empties into the duodenum (the first part of the small intestine). The pancreatic juices and bile help further digest food in the duodenum after food has left the stomach.

The pancreas is also part of the hormonal system and makes insulin and other hormones. Hormones made in the pancreas enter the bloodstream and help your body use or store the energy (sugar and fat) from the food you eat.

Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress–Related Genes

1. Arkaitz Carracedo1,
2. Meritxell Gironella2,
3. Mar Lorente1,
4. Stephane Garcia2,
5. Manuel Guzmán1,
6. Guillermo Velasco1, and
7. Juan L. Iovanna2

Abstract

Pancreatic adenocarcinomas are among the most malignant forms of cancer and, therefore, it is of special interest to set new strategies aimed at improving the prognostic of this deadly disease. The present study was undertaken to investigate the action of cannabinoids, a new family of potential antitumoral agents, in pancreatic cancer. We show that cannabinoid receptors are expressed in human pancreatic tumor cell lines and tumor biopsies at much higher levels than in normal pancreatic tissue. Studies conducted with MiaPaCa2 and Panc1 cell lines showed that cannabinoid administration (*a*) induced apoptosis, (*b*) increased ceramide levels, and (*c*) up-regulated mRNA levels of the stress protein p8. These effects were prevented by blockade of the CB_2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis *de novo*. Knockdown experiments using selective small interfering RNAs showed the involvement of p8 via its downstream endoplasmic reticulum stress–related targets activating transcription factor 4 (ATF-4) and TRB3 in Δ^9-tetrahydrocannabinol–induced apoptosis. Cannabinoids also reduced the growth of tumor cells in two animal models of pancreatic cancer. In addition, cannabinoid treatment inhibited the spreading of pancreatic tumor cells. Moreover, cannabinoid administration selectively increased apoptosis and TRB3 expression in pancreatic tumor cells but not in normal tissue. In conclusion, results presented here show that cannabinoids lead to apoptosis of pancreatic tumor cells via a CB_2 receptor and *de novo* synthesized ceramide-dependent up-regulation of p8 and the endoplasmic reticulum stress–related genes *ATF-4* and *TRB3*. These findings may contribute to set the basis for a new therapeutic approach for the treatment of pancreatic cancer. (Cancer Res 2006; 66(13): 6748-55)

http://cancerres.aacrjournals.org/content/66/13/6748.short

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Cannabinoids in pancreatic cancer: Correlation with survival and pain

Christoph W. Michalski,[1,2,*] Florian E. Oti,[2] Mert Erkan,[1,2] Danguole Sauliunaite,[1,2] Frank Bergmann,[3] Pal Pacher,[4] Sandor Batkai,[4] Michael W. Müller,[1,2] Nathalia A. Giese,[2] Helmut Friess,[1,2] and Jörg Kleeff[1,2]
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Abstract

Cannabinoids exert antiproliferative properties in a variety of malignant tumors, including pancreatic ductal adenocarcinoma (PDAC). In our study, we quantitatively evaluated the immunoreactivity for cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors as well as for the endocannabinoid metabolizing enzymes fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MGLL). Furthermore, quantitative real-time RT-PCR for CB1, CB2, FAAH and MGLL in normal pancreas and pancreatic cancer tissues was performed. Levels of endocannabinoids were determined by liquid chromatography/mass spectrometry. Immunoreactivity scores and QRT-PCR expression levels were correlated with the clinico-pathological (TNM, survival, pain) status of the patients. Evaluation of endocannabinoid levels revealed that these remained unchanged in PDAC compared to the normal pancreas. Patients with high CB1 receptor levels in enlarged nerves in PDAC had a lower combined pain score (intensity, frequency, duration; $p = 0.012$). There was a significant relationship between low CB1 receptor immunoreactivity or mRNA expression levels ($p = 0.0011$ and $p = 0.026$, respectively), or high FAAH and MGLL cancer cell immunoreactivity ($p = 0.036$ and $p = 0.017$, respectively) and longer survival of PDAC patients. These results are underlined by a significant correlation of high pain scores and increased survival ($p = 0.0343$). CB2 receptor immunoreactivity, CB2 receptor, FAAH and MGLL mRNA expression levels did not correlate with survival. Therefore, changes in the levels of endocannabinoid metabolizing enzymes and cannabinoid receptors on pancreatic cancer cells may affect prognosis and pain status of PDAC patients.

Cannabinoids for Cancer Treatment: Progress and Promise

. **Sami Sarfaraz, Vaqar M. Adhami, Deeba N. Syed, Farrukh Afaq, and Hasan Mukhtar**

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Author Affiliations

. Chemoprevention Program, Paul P. Carbone Comprehensive Cancer Center and Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin

. **Requests for reprints:**Hasan Mukhtar, Department of Dermatology, University of Wisconsin-Madison, 1300, University Avenue, Medical Sciences Center, B-25, Madison, WI 53706. Phone: 608-263-3927; Fax: 608-263-5223; E-mail: hmukhtar@wisc.edu.

Next Section

Abstract

Cannabinoids are a class of pharmacologic compounds that offer potential applications as antitumor drugs, based on the ability of some members of this class to limit inflammation, cell proliferation, and cell survival. In particular, emerging evidence suggests that agonists of cannabinoid receptors expressed by tumor cells may offer a novel strategy to treat cancer. Here, we review recent work that raises interest in the development and exploration of potent, nontoxic, and nonhabit forming cannabinoids for cancer therapy. [Cancer Res 2008;68(2):339–42]

http://cancerres.aacrjournals.org/content/68/2/339.full

Cell Death Dis. 2011 Apr 28;2:e152. doi: 10.1038/cddis.2011.36.

Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism.

Donadelli M, Dando I, Zaniboni T, Costanzo C, Dalla Pozza E, Scupoli MT, Scarpa A, Zappavigna S, Marra M, Abbruzzese A, Bifulco M, Caraglia M, Palmieri M.

Source

Department of Life and Reproduction Sciences, Biochemistry Section, University of Verona, Verona, Italy.

Abstract

Gemcitabine (GEM, 2',2'-difluorodeoxycytidine) is currently used in advanced pancreatic adenocarcinoma, with a response rate of < 20%. The purpose of our work was to improve GEM activity by addition of cannabinoids. Here, we show that GEM induces both cannabinoid receptor-1 (CB1) and cannabinoid receptor-2 (CB2) receptors by an NF-κB-dependent mechanism and that its association with cannabinoids synergistically inhibits pancreatic adenocarcinoma cell growth and increases reactive oxygen species (ROS) induced by single treatments. The antiproliferative synergism is prevented by the radical scavenger N-acetyl-L-cysteine and by the specific NF-κB inhibitor BAY 11-7085, demonstrating that the induction of ROS by GEM/cannabinoids and of NF-κB by GEM is required for this effect. In addition, we report that neither apoptotic nor cytostatic mechanisms are responsible for the synergistic cell growth inhibition, which is strictly associated with the enhancement of endoplasmic reticulum stress and autophagic cell death. Noteworthy, the antiproliferative synergism is stronger in GEM-resistant pancreatic cancer cell lines compared with GEM-sensitive pancreatic cancer cell lines. The combined treatment strongly inhibits growth of human pancreatic tumor cells xenografted in nude mice without apparent toxic effects. These findings support a key role of the ROS-dependent activation of an autophagic program in the synergistic growth inhibition induced by GEM/cannabinoid combination in human pancreatic cancer cells.

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